Reduced Brain Electric Activity and Functional Connectivity in Bipolar Euthymia: An sLORETA Source Localization Study

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Abstract: Bipolar disorder (BD) is a chronic illness with a relapsing and remitting time course. Relapses are manic or depressive in nature and intermitted by euthymic states. During euthymic states, patients lack the criteria for a manic or depressive diagnosis, but still suffer from impaired cognitive functioning as indicated by difficulties in executive and language-related processing. The present study investigated whether these deficits are reflected by altered intracortical activity in or functional connectivity between brain regions involved in these processes such as the prefrontal and the temporal cortices. Vigilance-controlled resting state EEG of 13 euthymic BD patients and 13 healthy age- and sex-matched controls was analyzed. Head-surface EEG was recomputed into intracortical current density values in 8 frequency bands using standardized low-resolution electromagnetic tomography. Intracortical current densities were averaged in 19 evenly distributed regions of interest (ROIs). Lagged coherences were computed between each pair of ROIs. Source activity and coherence measures between patients and controls were compared (paired t tests). Reductions in temporal cortex activity and in large-scale functional connectivity in patients compared to controls were observed. Activity reductions affected all 8 EEG frequency bands. Functional connectivity reductions affected the delta, theta, alpha-2, beta-2, and gamma band and involved but were not limited to prefrontal and temporal ROIs. The findings show reduced activation of the temporal cortex and reduced coordination between many brain regions in BD euthymia. These activation and connectivity changes may disturb the continuous frontotemporal information flow required for executive and language-related processing, which is impaired in euthymic BD patients.

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Title: Reduced brain electric activity and functional connectivity in bipolar euthymia – an sLORETA source localization study.

Short title: Brain activity in bipolar euthymia.

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Introduction

Bipolar disorder (BD) is a chronic illness with relapsing and remitting phases. Relapses are manic or depressive in nature. Manic episodes are characterized by elevated or irritable mood, agitation, decreased need for sleep, racing thoughts, and impulsive or high-risk behaviors[1,2]. Depressive episodes are characterized by persistent feelings of sadness, irritability, or anger, loss of interest in previously enjoyed activities, excessive or inappropriate guilt, hopelessness, sleep disturbances, problems concentrating, and thoughts of death or suicidal ideation. In severe cases, the individual may also develop symptoms of psychosis including delusions and hallucinations[1,2].

Approximately 1% of the worldwide population suffers from Bipolar disorder (BD) [3]. Affected individuals spend half of their time in active that is depressive or manic episodes. However, the other half of their time, they spend in a so-called euthymic state [4]. During the euthymic state, patients do not meet the full diagnosis of a manic or depressive episode, however, the illness is still present, and patients suffer from pressing and burdening cognitive and functional deficits [5-10].

Given the degree of functional impairment that persists in the euthymic state, it is most critical to also identify the underlying neural mechanisms. These mechanisms can be investigated via various means. An approach particularly sensitive to functional changes in neural activity is electroencephalography (EEG). EEG recordings allow the measurement of brain electric activity non-invasively on the scalp / head-surface at a high temporal resolution. Advanced analyses methods allow the identification of the cortical areas that exhibit the electric activity measured on the head surface and their functional connectivity.

A series of EEG studies have examined the brain physiological characteristics particular to BD. They primarily investigated brain electric activity during acute episodes and either compared manic and depressive episodes within BD patients [11] or compared BD patients during depressed [12] or manic [13] episodes with healthy controls. Comparing episodes within patients revealed increased fronto-temporal theta activity and decreased fronto-parietal beta activity during manic compared to depressive states [11].

Comparing patients to controls revealed anterior delta through alpha power decreases and anterior beta increases in depressed and left alpha power decreases in manic patients compared to controls [12,13].

Few studies investigated whether electrophysiological changes in BD compared to healthy controls persist during remission or so-called euthymic states. One study reported delta through beta power increases in the resting state EEG in BD patients in a euthymic state compared to healthy controls [14], while another one reported alpha power decreases[15]. Further studies investigated event related potentials (ERPs) [16-20] - for a review see [21] - and identified altered brain responses in euthymic patients compared to healthy controls. They comprised the theta, alpha, and beta frequency bands and were associated with functional impairments in fundamental dimensions of information processing such as cognitive flexibility, executive functions, and working memory [19]. We note that the extent of these electrophysiological changes was sometimes affected by particular medications such as lithium [20].

In recent years, a growing body of scientific investigations showed that beyond local and global brain electric power, it is essential to investigate how brain regions interact during different states of health and disease. Ultimately, healthy brain functioning relies on the dynamic interplay between specific brain regions rather than isolated activity increases or decreases.

To detect alterations in the interaction between brain regions, measures of functional connectivity may be used. A recent review identified eight EEG studies that assessed brain functional connectivity in BD[22]. However, only two of these studies included euthymic patients [23,24]. During the euthymic phase of BD patients resting state EEG functional connectivity in the delta band was increased across a broad range of brain regions [23] compared to healthy controls, whereas in an oddball paradigm event-related gamma coherence was decreased particularly between left and right fronto-temporal areas [24].

Many of these previous studies calculated EEG parameters from head-surface recorded signals, which does not allow direct inferences about the activity of the underlying brain regions. The remedy is to use an inverse solution algorithm, which has been theoretically and empirically validated, to localize intracortical source signals derived from the head-surface recordings prior to the computation of

measures of brain electric power or functional connectivity [25]. An additional problem arises regarding connectivity measures such as coherence, based on these estimated intracortical signals, in that they are biased and affected by low spatial resolution and volume conduction, see e.g. [26]. In the present study, use is made of an optimal unbiased connectivity estimator, known as "lagged connectivity", defined in [27,28]. Lagged connectivity is a measure of physiological connectivity, unaffected by the zero-lag artifact due to volume conduction. Its detailed derivation can be found in [27,28] and empirical and theoretical proof of its optimality properties can be found in [29]. Please note that all source codes and data for this proof are freely and openly available [29].

The present study investigated differences in intra-cortical activity and intra-cortical functional connectivity during eyes closed resting state in BD patients during euthymia and healthy controls.

Previous reports suggest that attention, executive function, and language processing are impaired across all phases of BD including euthymia e.g. [30,31]. For this reason, we expected changes in and between brain regions reportedly involved in these functions such as frontal and temporal [32-35] regions.

Materials and Methods

Participants

EEG recordings of twenty-six participants (13 patients, 13 controls) were retrospectively analyzed.

The patient group comprised 13 right-handed individuals (4 males, 9 females) that were diagnosed with 'Bipolar Disorder I' (BD) based on the SCID-I structured interview [36] according to DSM-IV [2]. The mean time since diagnosis was 4.25 years (*SD* = 4.31). Patients were between 24 and 54 years old (*M* = 34.23, *SD* = 8.33) and euthymic at the time of the EEG recording [(score ≤ 6 on the Young Mania Rating Scale YMRS [37] and score ≤ 8 on the 21-items version of the Hamilton Depression Rating Scale HAM-D [38]]. All patients were organically healthy as documented by physical examination and routine laboratory tests and received their treatment-as-usual medication. Four patients took antidepressants (sertraline,

bupropion, amitriptyline and/or venlafaxine), five anticonvulsants (lamotrigine, valproic acid), two lithium and seven antipsychotics (olanzapine, risperidone, ziprasidone and/or quetiapine).

The control group comprised 13 age- and sex-matched healthy individuals (four males, nine females). They were between 24 and 54 years old (*M* = 34.00, *SD* = 8.55) and were recruited by advertisements in local newspapers. Healthy controls reported to not be taking any medication or drugs and displayed no signs of physical, neurological, or mental illness.

This study was carried out in accordance with the Helsinki Declaration and approved by the Ethics Committee of the Medical University of Graz, Austria (Project Nr. 24-020ex11/12).

EEG recording

Nineteen-channel EEG was obtained from the following sites: Fp1/2, F7/8, F3/4, Fz, T3/4, C3/4, Cz, T5/6, P3/4, Pz, O1/2 International 10/20 System [39]. Head-surface electrodes were referenced to average mastoids. Two additional channels recorded vertical and horizontal eye movements. An Alpha-trace digital EEG TC-32 polygraph (Grossegger & Drbal GmbH, Vienna, Austria) was used recording 256 samples/s/channel and a band-pass filter set to 0.3–70 Hz.

EEG recordings were conducted during vigilance-controlled resting. Participants were comfortably seated in a chair and were instructed to close their eyes for the upcoming EEG recording. The technician alerted the patient with a gentle tone if the EEG showed signs of drowsiness ('vigilance-controlled resting'). The EEG was recorded for 20 min between 10 and 12 a.m.

Data pre-processing

EEG recordings were pre-processed using the Brain Vision Analyzer. Eye, muscle, and technical artifacts were rejected manually by visual inspection. EEG data were then segmented into artefact-free two-second epochs and re-referenced to average reference. Only epochs of the first 10 min of the recording were used for the analyses. On average participants contributed with 187.9 (SD= 91.0) 2-s epochs.

sLORETA Current Density

Intracortical standardized current densities in 6239 cortical voxels (spatial resolution: 5 mm) in eight frequency bands of two-second epochs were estimated with Standardized Low-Resolution Brain Electromagnetic Tomography (sLORETA) 40 (freely available from: www.uzh.ch/keyinst/loreta.htm). The frequency bands used correspond to the ones identified by 41,42 via factor analysis: delta (1.5-6 Hz), theta (6.5-8 Hz), alpha-1 (8.5-10 Hz), alpha-2 (10.5-12 Hz), beta-1 (12.5-18 Hz), beta-2 (18.5-21 Hz), beta-3 (21.5-30 Hz) and additionally, gamma (35-44 Hz). For each participant and each frequency band, intracortical current densities were voxel-wise averaged across two-second epochs. Technical details on the frequency domain analysis of cortical signals of electric neuronal activity can be found in Frei, Gamma 43.

For each participant, sLORETA intracortical current densities were frequency-band wise normalized. The log-transformed intracortical current densities were compared between patients and controls (voxel-wise comparison; unpaired t-tests). Statistical thresholds corrected for multiple testing ($p<0.05$, two-tailed; non-parametric randomization procedure 44) were applied. For each voxel significantly different between patients and controls, the corresponding Brodmann area was identified 45.

sLORETA- Intracortical Lagged Coherence

Brain electric functional connectivity was computed as intracortical lagged connectivity between all distinct pairs of 19 regions of interest (ROIs) following the procedure in [46] and [47]. To explore the functional connectivity between all major areas of the brain, we defined the ROIs based on the cortical areas underlying the 19 standard electrode positions / sites of our recordings. For each head-surface electrode site, the nearest cortical voxel was identified, and this voxel together with all voxels within a radius of 20 mm were assigned to the respective ROI. In this way ROIs were defined and were not based on the predefined Brodmann areas implemented in LORETA. This procedure resulted in 19 ROIs of cortical areas well-documented in other low resolution tomographies such as e.g. “Near Infrared Spectroscopy and Imaging” (NIRS) [48]. For each ROI the centroid of all included voxels was computed and attributed to the

corresponding Brodmann area (BA). Table 1 lists the centroid coordinates and the BAs contributing with at least five voxels to the ROIs. It should be noted that this particular choice of ROIs covers all major brain regions, as was originally intended with the definition of the 10/20 system. Furthermore, these 19 regions are in close proximity to the main nodes that form parts of the major resting state networks [49].

Table 1. Region of interest characteristics: seeds, centroid coordinates and contributing Brodmann areas.

	ROI centroid coordinates			BAs contributing to ROIs	
ROI seeds	X	Y	Z	left	right
Fp1	-23	57	-5	**10**,11	-
Fp2	23	58	-5	-	**10**,11
F7	-44	36	-8	11, **47**	-
F3	-35	42	27	9,**10**,46	-
Fz	5	41	45	-	6,**8**,9
F4	36	41	28	-	8,9,**10**,46
F8	44	36	-9	-	11,**47**
T7/T3	-60	-17	-14	20,**21**,22	-
C3	-45	-22	54	2,**3**,4,6,40	-
Cz	5	-10	64	-	**6**,24
C4	49	-22	50	-	**1**,2,3,4,6,40
T8/T4	63	-22	-9	-	20,**21**,22
P7/T5	-54	-61	-9	19,20,21,**37**	-
P3	-37	-67	43	**7**,19,39,40	-
Pz	-6	-60	59	5,**7**	-
P4	41	-65	43	-	**7**,19,39,40
P8/T6	51	-66	1	-	18,19,**37**,39
O1	-17	-93	9	17,18,**19**	-
O2	16	-93	6	-	17,**18**,19

Abbreviations: ROI, region of interest; BA, Brodmann area. Bold numbers indicate Brodmann areas containing the ROI centroid voxel.

For each participant and each frequency band, mean current densities within a given ROI were computed. Based on these means, intracortical lagged connectivity was computed between all 19 ROIs (with sLORETA) resulting in 171 intracortical lagged connectivity values (19*18/2).

As mentioned in the introduction, simple classical connectivity measures such as coherence, are biased and affected by low spatial resolution and volume conduction, see e.g. [26]. Several solutions to this problem have been proposed, some examples of which are the imaginary part of the coherence [26], the phase lag index [50], the weighted phase lag index [51], and lagged coherence [27,28], to name but a few. These methods were recently analyzed and compared exhaustively [29], and it was shown that the lagged coherence, besides being invariant to any amount of volume conduction, it also outperformed the other methods in detecting true physiological connectivity.

Connectivity was compared between patients and controls (unpaired t-tests) and statistical thresholds corrected for multiple testing ($p<0.05$, two-tailed; non-parametric randomization procedure [44] were applied.

Due to its approximate Gaussian distribution, intracortical lagged functional connectivity F_{lag} (sLORETA software option "linear lagged connectivity") rather than intracortical lagged coherence r^2_{lag} was computed. The two measures are related [$r^2_{lag}=1–\exp(-F_{lag})$]. Lagged connectivity had been successfully applied to compare inter- and intra-individual connectivity, e.g. schizophrenics versus controls: [28,46]; meditation/breath counting versus resting: [47,52].

To illustrate the major spatial tendency [52] common to all functional connections different between the two groups, we computed the 'principal functional connectivity'. Basically, the principal functional connectivity is a PCA-based topographical analysis of the functional connections differing between the groups, indicating the 'main' axis of these connections, i.e. their major spatial tendency (for a detailed description see [52]. Computations were done separately for each EEG frequency band and separately considered all connectivity pairs significantly increased or decreased between the groups.

Results

sLORETA Current Density

Patients showed significantly decreased intracortical current density compared to healthy controls in all eight EEG frequency bands (Figure 1); there were no significant increases in intracortical current density in any frequency band. Table 2 lists the number of voxels significantly differing between patients and controls (corrected for multiple testing, t>4.899) per BA and frequency band. Only BAs with at least 10 significantly differing voxels are listed. Reductions concerned primarily the temporal cortex (BAs 20, 21, 22, 36, 37, 41, 42) and both hemispheres in the delta, alpha-2, beta-1 and beta-2 band, but only the left hemisphere in the theta, alpha-1, beta-3, and gamma band. In the delta band, the temporal cluster showing decreased activity in patients extended to the postcentral region (BA 43). And part of the insula (BA 13) also showed activity decreases in the delta (both hemispheres) and beta-3 (left hemisphere) band.

Table 2. Number of voxels differing between patients and controls per Brodmann area and frequency band.

	Delta		Theta		Alpha-1		Alpha-2		Beta-1		Beta-2		Beta-3		Gamma	
BA	LH	RH	LH	RH	LH	RH	LH	RH	LH	RH	LH	RH	LH	RH	LH	RH
13	37	33	-	-	-	-	-	-	-	-	-	-	12	-	-	-
19	-	-	-	-	-	-	14	26	-	-	-	-	-	-	-	-
20	78	66	50	-	25	-	34	38	64	54	51	13	63	-	15	-
21	64	59	49	-	-	-	14	15	68	69	72	29	54	-	-	-
22	54	43	35	-	-	-	-	15	61	45	40	17	41	-	-	-
36	18	20	15	-	12	-	22	-	12	-	12	-	14	-	12	-
37	28	27	20	-	23	-	71	61	39	45	30	-	33	-	-	-
40	13	-	-	-	-	-	-	-	13	14	-	-	22	-	-	-
41	26	22	23	-	-	-	-	-	20	14	15	-	21	-	-	-
42	17	22	16	-	-	-	-	-	19	16	16	11	22	-	-	-
43	13	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: BA, Brodmann area; LH, left hemisphere; RH, right hemisphere.

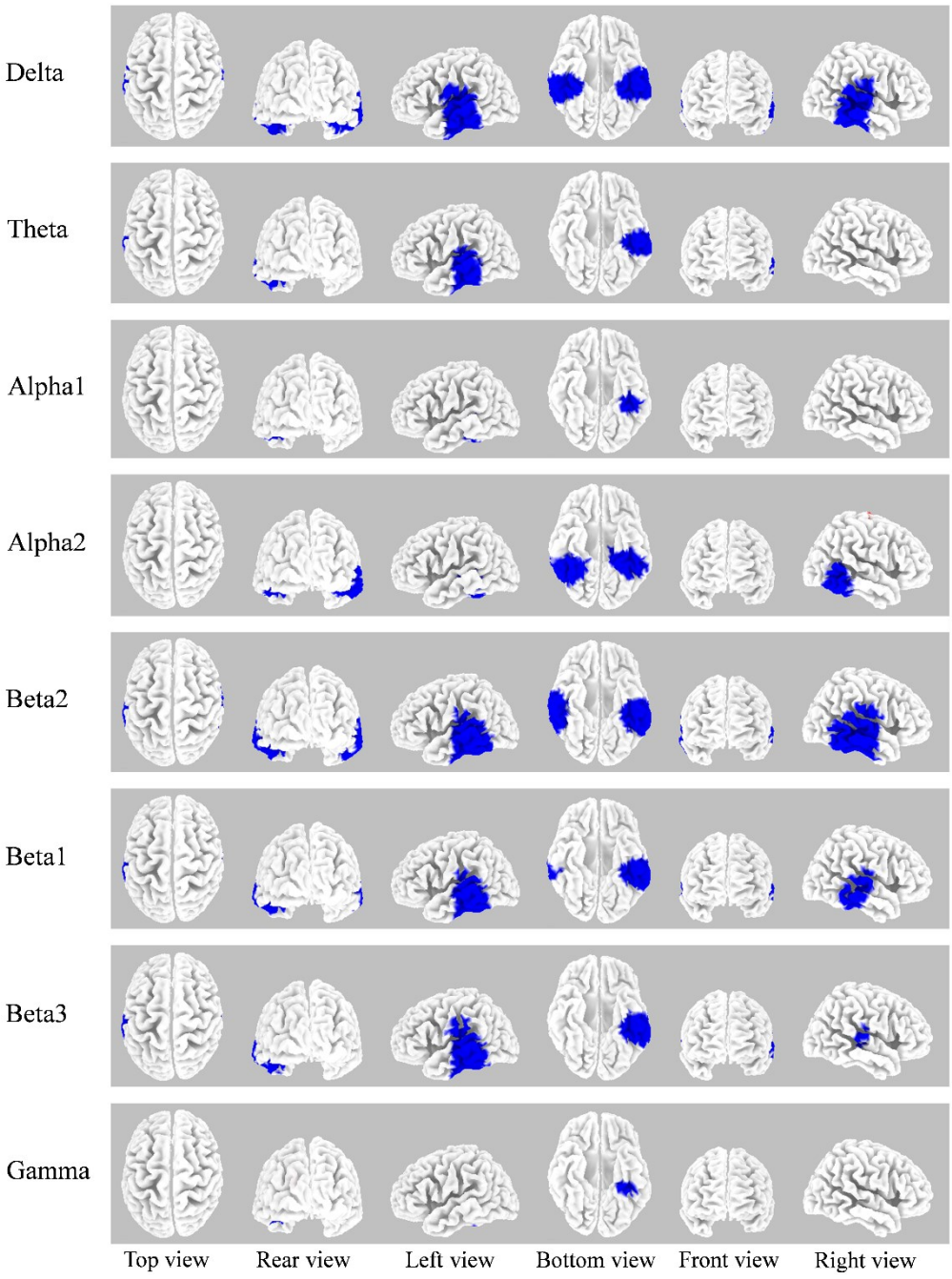

Figure 1. sLORETA images depicting brain areas with significantly decreased current density in BD patients compared to healthy controls of eight frequency bands (rows). No frequency band showed any areas with increased current density in BD patients compared to healthy controls.

sLORETA Intracortical Lagged Connectivity

Intracortical lagged connectivity was also reduced in patients compared to controls ($p<0.05$, corrected for multiple testing). These reductions concerned five frequency bands: delta, theta, alpha-2, beta-2, and gamma (Table 3). The brain regions showing reduced connectivity in patients varied across frequency bands (Figure 2A), in some cases (e.g. delta) with a local or sparse pattern, and in beta-2 with a more global pattern. The following descriptions are based on the affected ROIs and their contributing BAs (see Table 1): Reduced connectivity primarily concerned connections between pre-frontal (BAs 10 and 11) and right posterior regions (BAs 39 and 40) in the delta band, between left and right posterior regions (BAs 37, 39 and 19) in the theta band, between left frontal and right posterior (BAs 37, 39, 40, 7) regions in the alpha-2 band, between left frontal and bilateral posterior regions in the beta-2 band, and between left frontal (BAs 10, 11 and 47) and posterior regions in the gamma band.

Principal functional connectivity of the five affected frequency bands revealed a general anterior-posterior axis of connectivity reduction in the delta, beta-2, and gamma band, a left-right hemispheric axis of connectivity reduction in the theta band, and a diagonal axis (left frontal - right posterior) in the alpha-2 band (Figure 2B).

Table 3. Number of connections with significantly altered strength between patients and controls.

comparison	Delta	Theta	Alpha-1	Alpha-2	Beta-1	Beta-2	Beta-3	Gamma	**Total**
patients > controls	-	-	-	-	-	-	-	-	**0**
patients < controls	5	10	-	9	-	28	-	12	**64**

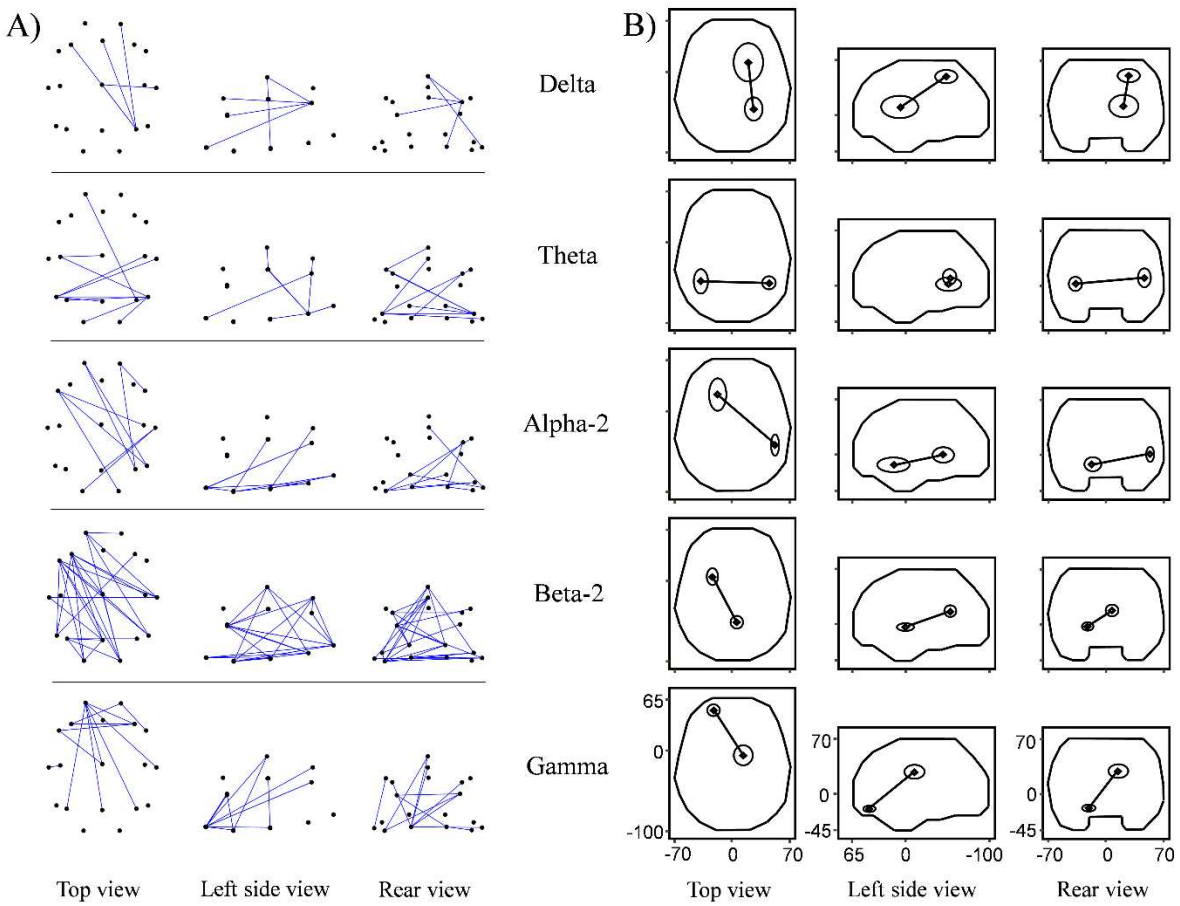

Figure 2. A) The 19 ROIs and the significantly reduced connections in patients compared to controls (blue lines). Only the five frequency bands (rows) showing reductions are illustrated. For the definition of the ROIs see Methods and Table 1. B) Glass brain views showing the mean locations of the principal functional connections and their standard errors (round shapes) for the five frequency bands (rows) showing reductions.

Discussion

The present study investigated differences in intra-cortical activity and intra-cortical functional connectivity during eyes closed resting between BD patients during euthymia and healthy controls. Based on reportedly impaired functions in BD euthymia involving attention, executive control, and language processing, we hypothesized electrophysiological changes in and between brain areas sub-serving these functions, such as frontal and temporal areas.

In line with our hypothesis, results revealed significantly altered resting intra-cortical activity in a large bilateral temporal cluster in BD patients compared to healthy controls. However, no frontal areas were affected in intra-cortical activity changes. The functional connectivity results though revealed significantly altered connectivity between temporal and frontal areas. Notably, functional connectivity changes were clearly not limited to the expected areas but affected the whole cortex. All observed changes were exclusively reductions in patients compared to controls. Intra-cortical activity was reduced in all EEG frequency bands and intra-cortical functional connectivity was reduced in the delta, theta, alpha-2, beta-2, and gamma frequency bands.

sLORETA Current Density

In line with our hypothesis, temporal areas showed reduced activity in euthymic BD patients during resting compared to controls.

The observed bilateral cluster of reduced activity in the temporal cortex, particularly the primary auditory cortex (BA 41, 42, 22) and the inferotemporal zone (BA 20, 21, 36 and BA 37) likely relate to the persistent deficiencies in language processing of BD patients during euthymia. The primary auditory cortex, which is located in the superior temporal lobe, together with the inferotemporal zone, which includes the middle, inferior temporal gyrus, and the hippocampal area are a decisive part of the bilaterally organized ventral stream of language processing [53-56]. They play a fundamental role in the decoding of speech and extraction of meaning [57,58], i.e. they are involved in semantic processing [59], as well as language comprehension and production [60]. Consequently, their reduced activity may account for the known deficits of euthymic BD patients in semantic processing [61,62], verbal episodic memory [63], verbal learning, and verbal working memory [64].

Temporal regions have not only been associated with language processing. They have been shown to be involved in executive functions as well [65,66], specifically through their interaction with the prefrontal cortex, a connection that we also found reduced in our connectivity analysis (see below). The impaired

functioning of the temporal regions may thus in part also account for the deficiencies in executive processing (such as verbal fluency, mental manipulation, working memory) of euthymic BD patients [10,31]. We note that it is also conceivable that the main functional changes observed might be the result of grey matter atrophy, i.e. reduced cortical thickness in the temporal lobes. Indeed, reduced temporal cortical thickness has frequently been reported in BD patients compared to controls [67-70].

Interestingly, our results revealed significantly reduced resting intra-cortical activity in slow (delta, theta), medium (alpha), and fast EEG frequency bands (beta, gamma) in euthymic BD patients compared to controls. The different EEG frequency bands have been associated with different functional roles ranging from inhibition, to routine processing and facilitation [42,71,72]. Consequently, our findings suggest that the brains of patients with BD during euthymic states have a reduced capacity to initiate both inhibitory, as well as excitatory brain processing in temporal regions. Presumably the interplay of both inhibitory and excitatory brain functions in these areas is vital to non-deficient language-related processing and a lack thereof is reflected in the observed deficiencies of euthymic BD patients.

Our results are in line with [15] who also observed alpha power decreases, but in conflict with [14] who reported delta through beta power increases. We note that these earlier studies, however, reported activity changes based on head-surface channel activity rather than source-specific activity changes. Moreover, different medications in different participant samples may also have affected the extent of the reported changes [20].

Davidson [73] has proposed that hemispheric asymmetry in prefrontal activation is related to reactivity to affectively valenced stimuli. Although we did not directly assess frontal alpha asymmetry in our subject groups, the lack of frontal differences in the alpha bands between patients and controls seems to imply that in our euthymic patients there is no difference in alpha-asymmetry compared to healthy controls. This is noteworthy, as relatively low left frontal activity has been reported in remitted depression [74-76]. Future studies are needed and of interest to evaluate alpha asymmetries in euthymic BD patients. As

alpha asymmetry is typically considered a trait marker [73,77], it is possible that it remains unaltered during euthymia.

sLORETA-Based Intracortical Lagged Connectivity

In line with our hypothesis, intra-cortical functional connectivity during resting between frontal and temporal areas were impaired in euthymic BD patients compared to controls. These changes were exclusively reductions in functional connectivity. Like the reduced intra-cortical activity, functional connectivity reductions concerned slow, medium, and fast EEG frequency bands (delta, theta, alpha-2, beta-2, and gamma). Furthermore, short-range, medium-range, and long-range connections were affected. The anterior-posterior major spatial tendency in the delta, beta-2, and gamma band, the left-right one in the theta band, and the diagonal one (left frontal - right posterior) in the alpha-2 band was reduced in BD patients.

Our results are in agreement with previous EEG [23,24] and fMRI-based [78-82] reports that also identified aberrant functional connections in BD euthymia. However, partly in contrast to our results, a magnetoencephalographic study [83] in euthymic BD patients reported increases in frontal synchronization in the delta band, but also frontal synchronization decreases in the beta band as we did. They only investigated frontal areas and used a different methodology which might explain the partly differing results.

The reduced connectivity over a broad frequency range is noteworthy. However, while a functional significance of EEG power or intra-cortical activity differences have been attributed to particular brain electric mechanisms [42,71,72], the interpretation of changes in functional connectivity in specific frequency ranges is not straight-forward. See also [84] for a recent review about fMRI connectivity studies in BD during clinical remission.

Irrespective of frequency, both unusually high as in epilepsy / seizure disorders: e.g. [85] and unusually low (as in schizophrenia [28,46,86]) functional connectivity between brain regions was observed.

Consequently, an ideal, intermediary extent of functional connectivity might be necessary for optimal or non-deficient cognitive processing.

Even though reduced connections in the different frequency bands concerned widespread brain areas, we observed the involvement of particular brain networks in patterns of altered functional connectivity that distinguished BD euthymia from controls. All affected frequency bands (delta, theta, alpha-2, beta-2, and gamma) comprised connectivity reductions between prefrontal (BAs 10, 11) and temporo-parietal (BAs 37, 39, 19, 40, 7) regions. These regions encompassed the superior and middle frontal gyrus, the superior and inferior temporal gyrus, the fusiform and angular gyri, and in the parietal cortex the angular gyrus, precuneus and inferior and superior parietal lobule. These areas are key components of brain networks that play an important role in self-referential processing, executive functions (such as attentional control, cognitive inhibition, inhibitory control, working memory, and cognitive flexibility), and emotional behavior as reflected in the default mode network (DMN) [87,88], the frontoparietal central executive network (CEN) [89], and the two ventral prefrontal networks (VPNs) [82], respectively. Therefore, our results are in line with previous reports that identified deficits in the DMN and CEN in BD [90-92] and functional connectivity reductions within the DMN during euthymic states in particular [78]. Moreover, they suggest that disturbances in the VPNs, which originate in the prefrontal cortex (ventrolateral BA 10 and 47 and ventromedial BA 11) and form iterative feedback loops with the amygdala and other limbic brain areas [93], may play a role in the dysregulation of emotional homeostasis that is responsible for the increased susceptibility towards intense mood changes [82] in BD patients.

The wide-spread functional connectivity decreases we observed in our BD euthymia patients suggests that many brain regions do not cooperate with each other to the extent that they do in healthy controls. This reduced cooperation [94] or coordination [95] may prevent a steady information flow between frontal and temporal areas that is required for the healthy functioning of cognitive processes that rely on the integration of information between these different brain regions. These processes likely exceed

language-processes and include attentional and executive control processing which are known to be impaired in BD patients during euthymia.

Limitations

Firstly, our BD patients were medicated (treatment-as-usual) and since medication affects the EEG in general e.g. [20,96-99], their medications could consequently have impacted our results. However, based on the key-lock principle [100,101], we would expect medication to normalize the brain state in parallel to the psychopathological state. Thus, remaining behavioral disturbances would be expected to be associated with corresponding brain functional changes. Moreover, since the patients were treated with various medications affecting EEG patterns in different ways [102] of patients with similar symptomatology, it is unlikely that medication effects could account for the observed differences. They rather reflect common changes of brain functional activity and connectivity across patients compared to controls.

Secondly, we examined spontaneous neural activity in euthymic BD patients and focused on brain function during no-task rest. Thus, because of the missing of neuropsychological tests, we cannot correlate our EEG results with neuropsychological data. It thus remains unclear whether disturbed electrophysiological brain function and possible underlying cognitive deficits are related to one another or not. Future investigations should help to elucidate this issue.

Thirdly, our results identified cross-sectional electrophysiological changes in BD euthymia and thus do not allow us to distinguish whether they reflect the primary disease process, compensation strategies, or a mixture of the two. Longitudinal studies are necessary to answer this question.

Fourthly, from a methods point of view, the small number of electrodes used is limiting the spatial resolution for the localization of activity and the separability of connectivity pairs with neighboring ROIs.

Finally, the methodology used in this study matches that of almost all functional localization and connectivity studies based on fMRI measurements. However, instead of computed BOLD signals of brain

activity, we use estimated signals of cortical electric neuronal activity, which have the major limitation of non-uniqueness and low spatial resolution.

Conclusions

To our knowledge, this is the first EEG study that investigated differences in intra-cortical source activation and source-based connectivity between euthymic BD patients and healthy controls. Our results demonstrate profound reductions of intra-cortical activity and functional connectivity in patients. They encompassed reductions in intra-cortical activity in temporal brain areas and wide-spread functional connectivity reductions in slow, medium, and fast EEG frequency bands. During so called "remission states" cognitive dysfunctions related to language-processing, attention regulation and executive functions often prevail [31]. Our results suggest that they may result from deficiencies in patients to upregulate both inhibitory and excitatory cortical activity in temporal areas and to coordinate activity across a manifold of brain regions including important nodes of the default mode network, the frontoparietal central executive network, and the two ventral prefrontal networks that have been associated with self-referencing, executive processes, and emotional regulation, respectively e.g. [89,103,104].

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Conflict of interest

The authors declare that they have no conflict of interest.

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